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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/981,460	KOHANE ET AL.	
	Examin r	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1,2 and 7-79* is/are pending in the application.

4a) Of the above claim(s) *25,28,34-36 and 41-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 7-24,26,27,29-33,37-40 and 45-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Pri rity under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim 71 has been rejoined in the previous office action. The statement concerning the withdrawal of claim 71 as set forth on the cover letter of the previous office action is a typographical error, and thus, has been vacated by the examiner. Claim 71, as currently amended, will be examined in this application.

Claims 1, 2, 65, 69, and 73 have been amended, claims 3-6, and 64 have been canceled, and claim 79 has been added by the amendment dated October 15, 2004.

Claims 25, 28, 34-36, 41-44, directed to non-elected species, remain withdrawn by the examiner. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Claims 1, 2, 7-24, 26, 27, 29-33, 37-40, 45-79, to which the following grounds remain and/or are applicable, are pending.

Newly amended claims 1, 2, 65, 69, and 73 introduce new matter into the as-filed application. Thus, following is a new matter rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 7-24, 26, 27, 29, 30-33, 37-40, 45-62, 65-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

Newly amended claims 1, 2, 65, 69, and 73, and claims dependent therefrom, introduce the phrase "wherein the lipid, protein, and sugar of the matrix are not part of a substantially cross-linked polymeric shell". The phrase does not find any explicit or implicit written support from the as-filed application. The examiner has considered applicant's response on page 13, which asserts about the implicit written support from the as-filed application. However, the response is not found persuasive. Applicant appears to assert that the preparation method as disclosed in the as-filed application is specific and does not disclose any step, which would achieve cross-linking of the matrix components. However, a close review of page 25 indicates otherwise. In fact, the paragraph immediately following the subsection entitled "Methods of Making Microparticles" clearly contemplates that "the inventive microparticles may be prepared using any method known in this art". Such is not the same as applicant's assertion, which argues that applicant at the time of filing invented a novel and specific preparation method, which stipulates that the components of the micropartiles can not be formulated as part of a cross-linked polymeric shell, let alone a "substantially cross-linked polymeric shell". Here is the reproduced section on page 25:

> Methods of Making Microparticles
>
> The inventive microparticles may be prepared using any method known in this art. These include spray drying, single and double emulsion solvent evaporation, solvent extraction, phase separation, simple and complex coacervation, and

other methods well known to those of ordinary skill in the art. A particularly preferred method of preparing the particles is spray drying. The conditions used in preparing the microparticles may be altered to yield particles of a desired size or property (e.g., hydrophobicity, hydrophilicity, external morphology, "stickiness", shape, etc.). The method of preparing the particle and the conditions (e.g., solvent, temperature, concentration, air flow rate, etc used may also depend on the agent being encapsulated and/or the composition of the matrix.

As such, the fact that there are no steps using heat, light, or ultrasound to effect cross-linking of the matrix components for form a "substantially" cross-linked polymeric shell in an exemplified disclosure of one of many 'know' preparation methods that applicant wish for the make and use of the claimed composition, does not necessarily mean that applicant has an 'implicit' written support for the subgenus as currently claimed, wherein a 'substantially' cross-linked polymeric shell is excluded from the originally filed claimed genus of a pharmaceutical composition comprising microparticles of a polynucleotide encapsulated in a matrix comprising lipid, protein, and sugar.

Thus, the new matter rejection is properly maintained.

In view of the lack of written support and/or definition for the phrase "substantially cross-linked polymeric shell", the phrase is also rejected under 35 USC 112, second paragraph, as set forth below.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 7-24, 26, 27, 29, 30-33, 37-40, 45-62, 65-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In base claims 1, 2, 65, 69, and 73, the "substantially" is indefinite because it is not apparent was to what is exactly the standard to measure the metes and bounds of the relative term. As such, one of skill in the art cannot ascertain as to what is considered to be a "substantially cross-linked polymeric shell".

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

In view of newly amended claims, which obviate the Grinstaff rejection of claims drawn to claimed embodiments, but now are limited to a subgenus of a composition comprising proteins such as albumin, a sugar (cellulose), a synthetic polymer such as PEG, and a phospholipid such as PC, all of which are main components of the claimed microparticles, all of which components are not part of a polymeric shell, the following rejection is a new ground of rejection, which is necessitated by applicant's amendment,

wherein the new ground of rejection concern claimed embodiments drawn at least to albumin, a sugar, a lipid, and optionally a synthetic polymer.

Claims 1, 2, 7-17, 20-24, 26, 27, 29-33, 37-38, 40, 45-47, 49-62, 65-70, 73-74, and 77-79 are rejected under 35 U.S.C. 102(b) as being anticipated by Sutton (US 6,204,054), or under 35 USC 103 as being unpatentable over (US 6,204,054).

The main thrust of the claimed invention is the making of a matrix or microparticle composed of at least three components selected from a lipid (DPPC, a protein (albumin) and a sugar (lactose). The microparticles can also be formulated so as to incorporate an excipient and/or stabilizer such as PEG or a synthetic polymer. The size of the microparticle can be less than 50 um (less than 10 um). The microparticles are employed for delivery of any known DNA of choice such as RNA, plasmid coding a protein of interest, *e.g*, protein of choice. The components must not be part of a polymeric shell.

Sutton teaches the making of a matrix or microparticle composed of at least three components selected from a lipid (lipids composed of a choline and a phospholipid such as DPPC, see line 6 of column 8), a protein (albumin, see lines 34-44 of column 3) and a sugar and/or a polymer such as PVP (lactose, see line 10 of column 7). Any bioactive agent or medicinal product, *e.g.,* DNA, see lines 7-54 of column 11. The size of the microparticle can be less than 50 um (less than 10 um, see lines 37-44 of column 8). Routes of administration are disclosed on lines 31-42 of column 7. The microparticles are employed for delivery of any known DNA of choice.

Followings are Sutton's most relevant reproduce passages as cited above:

The present invention provides transcytosis vehicles and enhancers capable of transporting physiologically-active agents across epithelia, endothelia and mesothelia containing the GP60 receptor. The GP60 receptor has been implicated in receptor-mediated transcytosis of albumin across cell barriers. By means of the invention, GP60 receptor-mediated transcytosis can be exploited for the transport of not only albumin, but also physiologically-active agents which do not naturally pass through epithelia, endothelia and mesothelia via the GP60 system.

Transcytosis vehicles and enhancers of the invention include albumin, albumin fragments, anti-GP60 polyclonal

[redacted]

Mammalian albumin is well known in the art and readily available. Preferably, the albumin used will be from the same mammalian species as the patient. For example, if the patient is human, human serum albumin will preferably be used as the transcytosis vehicle or enhancer. Similarly, if the patient is equine or bovine, equine or bovine serum albumin is preferably used, respectively.

Methods for conjugating the transcytosis vehicles of the present invention to a physiologically-active agent will be readily apparent to the skilled artisan and include, but are not limited to, glutaraldehyde conjugation involving Schiff base formation; carbodiimide reaction between proteins and carboxylic acids; acid anhydride activation of amine-containing drugs followed by carbodiimide linkage; activation of primary amine-containing drugs with 3-(2-pyridyldithio) propionate-N-succinimidyl anhydride followed by coupling to cysteine groups of proteins; coupling of sugar alcohols to proteins utilizing cyanuric chloride; and conjugation between amines and hydroxyl groups via bisperoxidation.

enhanced human albumin uptake 5-fold over the control. In a further embodiment of the present invention, delivery of active agents can be achieved when one of the transcytosis vehicle conjugates discussed above is administered together with one or more of the transcytosis enhancers of the present invention.

The transcytosis vehicle conjugates and the transcytosis enhancer compositions (including an active agent) of the present invention can be administered with a pharmaceutically-acceptable carrier or excipient, i.e., pharmaceutically-acceptable organic or inorganic substances suitable for application which do not deleteriously react with the conjugate or composition. Suitable pharmaceutically-acceptable substances include but are not limited to water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colourings, flavouring and/or aromatic substances, which do not deleteriously react with the conjugates. For parenteral application, particularly suitable preparations are solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages. For enteral application, particularly suitable preparations are tablets, dragees or capsules having a carrier binder such as talc and/or a carbohydrate, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

Administration of a conjugate or composition comprising one or more physiologically-active agents and one or more of the transcytosis vehicles or enhancers of the present invention can occur according to any art-known technique including injection or via the pulmonary airways. Injection is particularly suitable for administration to the vasculature and the peritoneum, whereas the pulmonary airways are particularly suitable for administration to the alveoli. Suitable formulations for pulmonary administration include one or more of the transcytosis enhancers of the present invention admixed with a physiologically-active agent. Alternative suitable formulations for pulmonary administration include a transcytosis vehicle conjugated to the agent. For example, formulations may be made from a nebulizer device such as an Acorn or DeVilbiss jet nebulizer, wherein the agent and transcytosis enhancer or vehicle are presented as an aqueous solution in the nebulizer reservoir. Alternatively, in a preferred embodiment for pulmonary administration, the formulation is discharged from a dry powder inhaler (DPI) device. DPI devices are described by Sutton et al in U.S. patent application Ser. No. 08/487,420 and in WO-9609814. They require spray-drying the formulation into microparticles of 2–5 μm which are preferred for alveolar penetration.

In particular, a transcytosis enhancer or vehicle of the present invention or a mixture thereof, preferably at a concentration of about 20% w/v, is used for spray-drying. The preparation to be sprayed may contain substances other than the transcytosis enhancers or vehicles and solvent or carrier liquid. For example, the aqueous phase may contain 1–20% by weight of water-soluble hydrophilic compounds such as sugars and polymers as stabilizers, e.g., polyvinyl

carrier liquid. For example, the aqueous phase may contain 1–20% by weight of water-soluble hydrophilic compounds such as sugars and polymers as stabilizers, e.g., polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), gelatin, polyglutamic acid and polysaccharides such as starch, dextran, agar, xanthin and the like.

use. Emulsifiers may be used (0.1–5% by weight), including most physiologically-acceptable emulsifiers, for instance egg lecithin or soya bean lecithin, or synthetic lecithins such as saturated synthetic lecithins, for example, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, or distearoyl phosphatidylcholine or unsaturated synthetic lecithins, such as dioleyl phosphatidylcholine or dilinoleyl phosphatidylcholine. Emulsifiers also include surfactants such as free fatty acids, esters of fatty acids with polyoxyalkylene compounds, e.g. polyoxypropylene glycol and polyoxyethylene glycol; ethers of fatty alcohols with polyoxyalkylene glycols; esters of fatty acids with polyoxyalkylated sorbitan; soaps; glycerol-polyoxyethylene ricinoleate; homo-and copolymers of polyalkylene glycols; polyethoxylated soya-oil and castor oil as well as hydrogenated derivative; ethers and esters of sucrose or other carbohydrates with fatty acids, fatty alcohols, these being optionally polyoxyalkylated; mono-, di- and triglycerides of saturated or unsaturated fatty acids, glycerides or soya-oil and sucrose.

hydrated fatty acids, glycerides of soya oil and sucrose.

Additives can be incorporated into the wall of the microspheres to modify the physical properties such as dispersibility, elasticity and water permeability. Among the useful additives include compounds which can "hydrophobize" the wall in order to decrease water permeability, such as fats, waxes and high molecular weight hydrocarbons. Additives which improve dispersibility of the microspheres in the injectable liquid-carrier are amphipathic compounds such as phospholipids; they also increase water permeability and rate of biodegradability. Additives which increase wall elasticity include plasticizers such as isopropyl myristate and the like. The quantity of additives to be incorporated in the wall is extremely variable and depends on the needs. In some applications, no additive is used at all; in other cases, amounts of additives which may reach about 20% by weight of the wall are possible.

number of small hollow particles.

The microparticles may comprise at least 50%, more preferably 70% or 80%, and most preferably 90%, by weight transcytosis enhancer. For use in an inhaler device, the microparticles may be formulated with a conventional excipient such as lactose or glucose. The amount of the physiologically-active agent will be chosen with regard to its nature and activity, to the mode of administration and other factors known to those of skill in the art. By way of example, the number of particles administered may be such as to deliver 100 mg/day α-1 anti-trypsin, or 0.1 mg/day of an active agent such as beclomethasone. Other possible physiologically-active agents that can be administered via microparticles are given below.

> By "physiologically-active agent" is intended drugs which include nucleic acid molecules and medicinal peptides and proteins. "Physiologically-active agent" is used interchangeably herein with "drug", "active", "active agent" and "therapeutic". Drugs that would benefit from a more rapid transcytosis across the endothelia and epithelia include Luteinizing hormone (LH), chorionic gonadotropin, atrial peptides, interferon, the various lymphokines such as the interleukins (I, II, III, IV, V, VI, and VII), and colony-stimulating factors.

With regard to the claimed limitations, wherein albumin and physiologically active agents are embedded in a microcapsule or microsphere composed of albumin and additional wall forming materials such as a phospholipids and a sugar, the following passage is cited to support such:

> In particular, a transcytosis enhancer or vehicle of the present invention or a mixture thereof, preferably at a concentration of about 20% w/v, is used for spray-drying. The preparation to be sprayed may contain substances other than the transcytosis enhancers or vehicles and solvent or carrier liquid. For example, the aqueous phase may contain 1-20% by weight of water-soluble hydrophilic compounds such as **sugars and polymers** as stabilizers, e.g., polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), gelatin, polyglutamic acid and polysaccharides such as starch, dextran, agar, xanthin and the like. Similar aqueous phases can be used as the carrier liquid in which the final microsphere product is suspended before use. Emulsifiers may be used (0.1-5% by weight), including most physiologically-acceptable emulsifiers, for instance egg lecithin or soya bean lecithin, or synthetic lecithins such as saturated synthetic lecithins, for example, **dimyristoyl phosphatidylcholine**, dipalmitoyl phosphatidylcholine, or distearoyl phosphatidylcholine or unsaturated synthetic lecithins, such as dioleyl phosphatidylcholine or dilinoleyl phosphatidylcholine. Emulsifiers also include **surfactants** such as free fatty acids, esters of fatty acids with polyoxyalkylene compounds, e.g. polyoxypropylene glycol and polyoxyethylene glycol; ethers of fatty alcohols with polyoxyalkylene glycols; esters of fatty acids with polyoxyalkylated sorbitan; soaps; glycerol-polyoxyethylene ricinoleate; homo-and copolymers of polyalkylene glycols; polyethoxylated soya-oil and castor oil as well as hydrogenated derivative; ethers and esters of **sucrose or other carbohydrates with fatty acids, fatty alcohols, these being optionally polyoxyalkylated; mono-, di- and triglycerides of saturated or unsaturated fatty acids, glycerides or soya-oil and sucrose**.
>
> Additives can be incorporated into the wall of the microspheres to modify the physical properties such as dispersibility, elasticity and water permeability. Among the useful additives include compounds which can "hydrophobize" the wall in order to decrease water permeability, such as fats, waxes and high molecular weight hydrocarbons. **Additives which improve dispersibility**

f the microspheres in the injectable liquid-carrier are amphipathic c mpounds such as ph sph lipids; they also increase water permeability and rate of biodegradability. Additives which increase wall elasticity include plasticizers such as isopropyl myristate and the like. The quantity of additives to be incorporated in the wall is extremely variable and depends on the needs. In some applications, no additive is used at all; in other cases, amounts of additives which may reach about 20% by weight of the wall are possible.

A solution containing one or more transcytosis enhancers or vehicles of the present invention and additive, if any, is atomized and spray-dried by any suitable technique which results in discrete microspheres or microcapsules of 2 to 5 .mu.m as discussed above. As used herein, **"microcapsules" refers to hollow particles enclosing a space, which space is filled with a gas or vapour but not with any solid materials**.
A further embodiment of the present invention is the co-spray-drying of the physiologically-active agent with the transcytosis enhancer in order to facilitate stabilization of the active agent during formulation, packing, and most importantly, during residence on the alveolar lining. In this environment, there can be intense proteolytic activity. In this or another embodiment, the active agent may be covalently linked to the transcytosis vehicle via cleavable linkages prior to spray-drying. This embodiment represents a method of carrying the active agent all the way from the device to the bloodstream, and possibly to targets within the body. The formation of particles with optimal aerodynamic size means that the "physical" vehicle delivers the active agent to the site of absorption. Once deposited upon the alveoli, the "molecular" vehicle then protects and facilitates passage into the bloodstream via the GP60-mediated transcytosis system and, once in the bloodstream, can further enhance circulatory half-life and even direct the active agent to certain sites which are found to contain the GP60 receptor. Suitable linking technologies are discussed above; further, WO-A-9317713 describes esterase-sensitive polyhydroxy acid linkers. Such technology, used in the derivatization of the transcytosis vehicle prior to spray-drying, enables the production of a covalent carrier system for delivery of active agents to the systemic vasculature. This utilizes the potential of the transcytosis vehicles to cross the alveoli and to carry active agents over a prolonged period while protecting potentially unstable entities.

Although the physiologically-active agent used in the present invention may be imbibed into or otherwise associated with the microparticles after their formulation, it is preferably formulated with the transcytosis vehicle or enhancer. The microparticles may be at least partly coated with a hydrophobic or water-insoluble material such as a fatty acid, in order to delay their rate of dissolution and to protect against hydroscopic growth.

Methods and equipment for spray-drying and generating the microparticles, e.g. for use in a dry powder inhaler device are described in more detail in WO-A-9609814 and in U.S. patent application Ser. No. 08/487,420, the contents of which are incorporated herein by reference.

Therefore, the Sutton reference as a whole particularly teaches that any combination of biocompatible materials, excipients, emulsifiers, and/or pharmaceutical acceptable excipients can be incorporated into an albumine based vesicles and/or enhancers, wherein all of the excipients/protector/albumin form microcapsules comprising a physiologically active agent conjugated to albumin or embedded in the

microparticles. The combinations of these components and additional excipients, stabilizers, flavoring substances, tablet based carriers are and techniques used to incorporate various components and/or combinations for optimization are considered to be well-established in the prior art, see column 9-10. As such, to the extent that the claims embrace various minor modifications including those of desire choice, *e.g.,* diameter, weight percentage of each of the components, DNA derivatives, modified sugars and/or modified lipids, such would have been obvious to one of ordinary skill in the art. A close review of the as-filed specification show that no unexpected result arise from any of these claimed combinations, and that components varying in weight percentage and/or components such as derivatived lipids are employed interchangeably in the prior art. Thus, it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed compositions. Likewise, the microparticles of Sutton would then be suitable to encapsulate and/or deliver any drug of choice such as DNA, RNA or plasmid coding for a protein or antigen of interest. As such, it would also have been obvious for one of ordinary skill in the art of polymer or microparticle to employ any combination of ratio or percent weight of each of the biocompatible material as a matter of design choice for the making of claimed composition, particularly since the reference clearly teaches that as long as albumin is employed, combinations of albumin, sugar, lipids and/or other excipients/stabilizers can be formulated to make a claimed vesicle or microparticle designed for use as a carrier of any biologically active molecules such as known antigen coding DNA, *e.g.,* plasmid, expression vectors, recombinant DNA(s). Notwithstanding the reasoning for rendering

the claimed invention as broadly claimed anticipated by Sutton, there clearly exists general art accepted motivations for formulating an excipient such as a protein, a sugar and/or a lipid such as DPPC into the albumin based polymer of Sutton. This general art accepted motivations are valid because of an absence of valid evidence showing unexpected results commensurate with the full breadth of the claimed invention.

Thus, the Sutton reference anticipates, or in the alternative, renders the claimed invention as a whole *prima facie* obvious.

Applicant's response has been considered (page 12-15) but is moot in view of the new ground of rejection.

Claims 1, 18, 19, and 73-76 are rejected under 35 USC 103 as being unpatentable over Sutton taken with Grinstaff.

The rejection of the base claims is applied here as indicated above in the 102 rejections.

To the extent that Sutton does not teach explicitly that the carriers or particles can be used to deliver a DNA coding for a protein antigen such as a viral or bacterial antigen, Grinstaff is one of many prior art of record that teaches that it is well established in the prior art that DNA immunogenic compositions can be used in combination with a polymeric or particle based carrier for enhancing the controlled release and bioavailability of an expressed antigen *in vivo.* See Example 13.

It would also have been obvious for one of ordinary skill in the art to employ the

albumin based carrier to deliver any DNA of choice such as a known antigen encoded DNA of choice. One of ordinary skill in the art would have been motivated to do so because the albumin based carrier is expected to enhance the transport and delivery of a DNA of choice to a target tissue *in vivo,* and because it is obvious to substitute for one another components that known in the prior art, whereby the albumin based carrier is expected to exert equivalent characteristics and/or functional effect to the intended delivery DNA of choice.

Thus, the claimed invention, as a whole, was *prima facie* obvious.

Claims 69, 71, 72 are rejected under 35 USC 103 as being unpatentable over Sutton taken with Wheeler (US 5,976,567).

The rejection of the base claims is applied here as indicated above in the 102 rejections.

To the extent that Sutton does not teach that the carriers or particles can be used to deliver a DNA coding for a protein, and that the carriers or particles can be used to transducer hematopoietic stem cells or embryonic stem cells *in vitro* and/or *in vivo,* Wheeler teaches that DPPC-based carriers (column 8, line 60) can be used to enhance the transfection and delivery of lipid/nucleic acids complexes into hematopoietic stem cells or embryonic stem cells *in vitro* and/or *in vivo* (column 28, lines 34-47).

It would also have been obvious for one of ordinary skill in the art to employ the albumin based carrier of Sutton to delivery and/or transducer embryonic stem cells *in vitro* or *in vivo.* One of ordinary skill in the art would have been motivated to do so

because it is well-established in the prior art, as exemplified by Wheeler, that a DNA delivery carrier or particle such as lipid based nucleic acid particles can be used to enhance the DNA delivery and transfection into embryonic stem cells *in vitro* and/or *in vivo*.

Thus, the claimed invention, as a whole, was *prima facie* obvious.

Applicants' comments (page 16 bridging page 17) also have been considered by the examiner but is not found persuasive for the same reasons as set forth in the stated rejections and the reasoning as addressed in the preceding paragraphs.

Furthermore, in order to support the examiner's rebut to applicant's response, the following references are further cited to indicate that it is well-established in the prior art of record that microparticles composed of at least three components selected from a sugar, protein, lipid and polymer are routinely made by a skilled artisan for a microparticle based delivery formulation:

1/ Hanes (US 5,855,913) teaches a polymeric microparticle of less than 10 um in diameter for use as a controlled release- encapsulated carrier of biologically active molecules such as DNA or DNA coding for a gene of interest, wherein the microparticles are composed of a combination of biocompatible materials selected from DPPC, copolymers, protein exipients (any known polymeric polyeptide or copolymers thereof) and a sugar (lactose), *e.g.,* entire disclosure including claims, column 3 bridging column 4, column 4 bridging column 5, entire column 6, column 6 bridging column 7, column 7, lines 4-68, column 8, lines 7-19, column 11 through column 12.

2/ Edwards (US 2004/0076589 A1) teaches on par. 0064 that microparticles composed of PLGA/DPPC/charged functional groups such as an amino acid can be made for delivery of a biologically active agent by aerosol. Batycky (US 6,586,008) teaches the same on columns 7 and 8.

3/ Sankaram (US 6,277,413) teaches polymeric matrix carrier composed of biodegradable polymers such as polypeptides and a synthetic polymer and lipids (columns 7 and 8).

4/ Unger (US 2001/0031740) teaches on claims 1,2 and 39 that lipid carriers bearing a sulfonated saccharide can be used as a delivery vehicle.

5/ Bellhouse (US 6,685,669) teaches on column 4 that a delivery composition comprising a carrier such as gelatin, excipients such as lactose, and a charged lipid is routinely made to deliver a therapeutic agent.

6/ Mori (US Pat No. 5,776,488) teaches on column 1 that it is well known in the prior art that lipsomal carriers comprising a fatty acid, PEG and a sugar have been made to encapsulate an anti-tumor agent.

7/ Rypacek (GB 2 174 097 A) teaches that a polymeric stabilizer such as a poly(alpha-amino acid) can be used in the making of spherical microparticles of starch dextran or human serum albumin (entire disclosure).

Claims 1, 2, 7-24, 26, 27, 29-31, 33, 37-40, 45-63, 65-69, 73-78 are rejected under 35 USC 103(a) as being unpatentable over Hanes (US 5,855,913).

Hanes teaches a polymeric microparticle of less than 10 um in diameter for use

as a controlled release- encapsulated carrier of biologically active molecules such as DNA or DNA coding for a gene of interest, wherein the microparticles are composed of a combination of biocompatible materials selected from DPPC, copolymers, protein excipients (any known polymeric polyeptide or copolymers thereof) and a sugar (lactose), *e.g.*, entire disclosure including claims, column 3 bridging column 4, column 4 bridging column 5, entire column 6, column 6 bridging column 7, column 7, lines 4-68, column 8, lines 7-19, column 11 through column 12.

Column 4 clearly states that the particles may be formed of biodegradable materials such as proteins in combination with a surfactant (DPPC):

particles generally have a mean diameter between 5 μm and 30 μm. The particles may be formed of biodegradable materials such as biodegradable polymers, proteins, or other water soluble or non-water soluble materials. Other examples include particles formed of water-soluble excipients, such as trehalose or lactose, or proteins, such as lysozyme or insulin. The particles incorporating a surfactant can be used for enhanced delivery of a therapeutic agent to the airways or the alveolar region of the lung. The particles may be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of a wide variety of therapeutic agents. They also optionally may be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 μm and 100 μm.

Surfactants which can be incorporated into particles to improve their aerosolization properties include phosphoglycerides. Exemplary phosphoglycerides include phosphatidylcholines, such as the naturally occurring lung surfactant, L-α-phosphatidylcholine dipalmitoyl ("DPPC"). The surfactants advantageously improve surface properties

Column 5:

As used herein, a particle "incorporating a surfactant" refers to a particle with a surfactant on at least the surface of the particle. The surfactant may be incorporated throughout the particle and on the surface during particle formation, or may be coated on the particle after particle formation. The surfactant can be coated on the particle surface by adsorption, ionic or covalent attachment, or physically "entrapped" by the surrounding matrix. The surfactant can be, for example, incorporated into controlled release particles, such as polymeric microspheres.

Surfactants known in the art can be used including any naturally occurring lung surfactant. Other exemplary surfactants include diphosphatidyl glycerol (DPPG); hexadecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; sorbitan trioleate (Span 85); glycocholate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; tyloxapol and a phospholipid.

Regarding blends of co-polymers of various types of polymers such as protein and polysaccarides, column 6 states:

Column 6:

Other polymers include polyamides, polycarbonates, polyalkylenes such as polyethylene, polypropylene, poly (ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly vinyl compounds such as polyvinyl alcohols, polyvinyl ethers, and polyvinyl esters, polymers of acrylic and methacrylic acids, celluloses and other polysaccharides, and peptides or proteins, or copolymers or blends thereof. Polymers may be selected with or modified to have the appropriate stability and degradation rates in vivo for different controlled drug delivery applications.

In one embodiment, aerodynamically light particles are formed from functionalized polyester graft copolymers, as described in Urkach et al., *Macromolecules*, 28:4736-4739 (1995); and Urkach et al., "Poly(L-Lactic acid-co-amino acid) Graft Copolymers: A Class of Functional Biodegradable Biomaterials" in *Hydrogels and Biodegradable Polymers for Bioapplications*, ACS Symposium Series No. 627, Raphael M. Ottenbrite et al., Eds., American Chemical Society, Chapter 8, pp. 93–101, 1996.

Regarding incorporations of additional polymeric materials, therapeutic agents, and/or

excipients such as gelatin (which is a protein) or a sugar into the particles (*emphasis added*), Hanes teaches:

> Optionally the particles may be formed of the surfactant plus a therapeutic or diagnostic agent. Different properties of the particle which can contribute to the aerodynamic lightness include the composition forming the particle, and the presence of irregular surface structure, or pores or cavities within the particle.
>
> Materials other than biodegradable polymers may be used to form the particles including other polymers and various excipients. The particles also may be formed of the drug or diagnostic agent and surfactant alone. In one embodiment, the particles may be formed of the surfactant and include a therapeutic agent, to improve aerosolization efficiency due to reduced particle surface interactions, and to potentially reduce drug loss due to phagocytosis by alveolar macrophages.
>
> Other materials include, but are not limited to, gelatin, polyethylene glycol, trehalose, and dextran. Particles with degradation and release times ranging from seconds to months can be designed and fabricated, based on factors such as the particle material.

In other words, Hanes suggests that any combination of biocompatible materials such as therapeutic agents, polymers, lipid surfactants and protein/sugar excipients can be used to make the encapsulated particles so that the particles are basically formulated to become polymeric microparticles for drug delivery to the pulmonary system, wherein the particles having an appropriate size such as at least 5 microns in diameter, and wherein the polymeric particles are capable of biodegrading at a controlled rate for delivery of a drug (see column 5, last full par.), and column 7 through column 8.

Hanes also teaches on column 6 (last par.) that the polymeric particles are preferably prepared by spray drying, and that the size of the particles can be between 5

and 30 um in diameter. Polymer and/or co-polymers concentrations can be used, for example, between 0.05 and 1.0 g/ml. Furthermore, Hanes teaches (columns 7-8) that depending on a preference of particularly desired aerodynamic properties of inhaled microparticles, the spray drying parametes such as concentrations of the surfactants, polymers and exipients can be adjusted accordingly by a person of ordinary skill in the art.

To the extent that Hanes do not teach explicitly minor modifications such as known DNAs, RNA or plasmids encoding for an antigen, ratios of agents being used in the formulations, and/or a particular combination of known matrix polymers, lipids and excipient(s), *e.g.,* sugar as an excipient added to DPPC/protein biodegradable based polymer or blends of various types of polymers including those of sugar and protein, such would have been obvious to one of ordinary skill in the art as minor modifications that can be practiced as a mater of design choice by a person of an ordinary skill in the art of polymer.

Thus, Hanes renders the claimed invention as a whole *prima facie* obvious.

Claims 1, 2, 7-24, 26, 27, 29-33, 37-40, 45-69, 73-79 are rejected under 35 USC 103 as being unpatentable over Hanes taken with any of Grinstaff, Sutton, or Rypacek, and further in view of Wheeler.

The rejection of the base claims are applied here as indicated above.

While Hanes do no claim explicitly minor modifications such as known DNAs, RNA or plasmids encoding for an antigen, ratios of agents being used in the

formulations, and/or a particular combination of known matrix polymers (albumin and/or other known polymer), lipids and excipient(s) such as any other sugar (cellulose), such would have been obvious to one of ordinary skill in the art as minor modifications that can be practiced as a mater of design choice by a person of an ordinary skill in the art of polymer, particularly in view of the totality of the prior art of record as set forth in Grinstaff, Sutton, or Rypacek, wherein each of which clearly teaches that a combination of a polymeric polypeptide such as albumin can be used in a combination of other polymer and/or suitable excipients such as lipid and/or sugar in order to make a suitable delivery microparticle composition for a delivery of choice.

Thus, it would have been obvious for one of ordinary skill in the prior art to employ albumin as an at least one of the suitable polymers in the making of polymeric microparticles of Hanes. One would have been motivated to do so because the totality of the prior art of record teaches that albumin can be used as a biodegradable material in the making of a polymeric microparticle.

It would also have been obvious for one of ordinary skill in the art to employ the polymeric shell of Grinstaff to delivery and/or transducer embryonic stem cells *in vitro* or *in vivo*. One of ordinary skill in the art would have been motivated to do so because it is well-established in the prior art, as exemplified by Wheeler, that lipid nucleic acid particles can be used to enhance the DNA delivery and transfection into embryonic stem cells *in vitro* and/or *in vivo*. See column 8, line 60, column 28, lines 34-47).

Thus, the claimed invention was *prima facie* obvious.

Applicant's response (pages 15-18) has been considered by the examiner, and is

found partially persuasive for the withdrawal of the 102 rejection, but is not found persuasive for the reasons as set forth in the above stated rejection and the following reasons:

Applicant mainly asserts on page 15 since Hances *et al.* nowhere teach or suggest the particular combinations of materials recited in the claims for use in the claims. The assertion is not found persuasive because when Hanes is considered as a whole in light of its disclosure and the totality of the state of the prior art, there clearly exists general art accepted motivations for formulating an excipient such as a sugar into the DPPC/protein/polymer blends of Hanes. This general art accepted motivations are valid because of an absence of valid evidence showing unexpected results commensurate with the full breadth of the claimed invention. Note that column 4 clearly states that the particles may be formed of biodegradable materials such as proteins or sugar (lactose) in combination with a surfactant (DPPC):

4

particles generally have a mean diameter between 5 μm and 30 μm. The particles may be formed of biodegradable materials such as biodegradable polymers, proteins, or other water soluble or non-water soluble materials. Other examples include particles formed of water-soluble excipients, such as trehalose or lactose, or proteins, such as lysozyme or insulin. The particles incorporating a surfactant can be used for enhanced delivery of a therapeutic agent to the airways or the alveolar region of the lung. The particles may be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of a wide variety of therapeutic agents. They also optionally may be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 μm and 100 μm.

> Surfactants which can be incorporated into particles to improve their aerosolization properties include phosphoglycerides. Exemplary phosphoglycerides include phosphatidylcholines, such as the naturally occurring lung surfactant, L-α-phosphatidylcholine dipalmitoyl ("DPPC"). The surfactants advantageously improve surface properties

Hanes additionally teaches that other excipients such as PEG, gelatin or trehalose can be included in the aforementioned microparticles, and that targeting agents such as lectin or hormones can be incorporated into the microparticles:

> Other materials include, but are not limited to, gelatin, polyethylene glycol, trehalose, and dextran. Particles with degradation and release times ranging from seconds to months can be designed and fabricated, based on factors such as the particle material.
>
> Exemplary targeting molecules include antibodies and fragments thereof including the variable regions, lectins, and hormones or other organic molecules capable of specific binding, for example, to receptors on the surfaces of the target cells.

Clearly, Hanes recognizes the desirability of incorporating exicpients and/or targeting agents into the DPPC/blended protein based polymer for improving and/or optimizing degradation rates and release times. As such, the above 103 rejection is appropriate.

Applicant further asserts that Hanes only teaches a combination of a surfactant in particles for drug delivery. However, such is not found persuasive because of the reasons as set forth in the preceding paragraphs. Applicant's assertion about the mistake of reciting Example 3 has been considered, and is found persuasive for the withdrawal of the 102 rejection. However, such does not impart the validity of the maintained 103 rejection. Applicant further asserts that Hanes does not teach or even

suggest a combination of three components such as a protein, sugar and a lipid. However, such is not found persuasive because of the preceding paragraphs.

Applicants further argue about the lack of an expectation of success, however, no evidence is found to indicate that one of ordinary skill in the art would have reasonably believed, particularly on the basis of the totality of the prior art, that there is not a reasonable expectation of success to arrive at the invention as broadly claimed. Furthermore, the fact that applicant shows that DNA were still retained in the microparticles comprising a particular combination of DPPC, albumin, and lactose at a particular concentration does not render the lack of a reasonable expectation of success in the making and use a DPPC/polymer based microparticles of Hanes for use in controlling the delivery of a DNA of choice *in vivo*. In fact, there is not a evidence found in the totality of the prior art to show that a DNA encapsulated in a polymeric microparticle of choice such as those comprising DPPC/protein/excipients was not as stable as a naked DNA when delivered *in vivo*. As such, applicant's argument is not found persuasive. Applicant also appears to assert that the previous office action was not specific enough to better explain the above stated rejection. To the extent that applicant's assertion is relevant to the remaining 103 rejection, such is not found persuasive because the previous office action does cite specific columns and lines from Hanes for supports regarding the claimed invention as broadly claimed. To further strengthen the prosecution history of this application, the passages from the cited lines and columns have been reproduced in the above stated rejections.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Central Fax number, which is **571-273-8300**.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

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